Introduction to Prostate Brachytherapy

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Prostate Cancer Death Rate
(American Cancer Society 2005)
Why the decline in incidence and mortality over the last 10 years?

- Improved treatment isn’t the only explanation.
- PSA screening allows diagnosis at earlier stages
  - Earlier stage disease is more curable regardless of improvements in technique or technology
  - Each year screening becomes more prevalent and each year the average patient presents with lower risk
  - Survival comparisons from one time interval to another are not valid because patient characteristics are substantively different.
<table>
<thead>
<tr>
<th>Stage</th>
<th>Description</th>
<th>Substage</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>cT1</td>
<td>Microscopic disease neither palpable nor visible on TRUS</td>
<td>cT1a</td>
<td>Incidental finding in ≤ 5% of tissue sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cT1b</td>
<td>Incidental finding in &gt; 5% of tissue sample</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cT1c</td>
<td>Found on needle biopsy due to ↑ PSA</td>
</tr>
<tr>
<td>cT2</td>
<td>Palpable tumor apparently confined within the prostate</td>
<td>cT2a</td>
<td>Involves ≤ half of one lobe of the prostate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cT2b</td>
<td>Involves &gt; half of one lobe of the prostate</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cT2c</td>
<td>Involves both lobes of the prostate</td>
</tr>
<tr>
<td>cT3</td>
<td>Tumor protrudes through the prostate capsule</td>
<td>cT3a</td>
<td>Extracapsular extension of one or both lobes</td>
</tr>
<tr>
<td></td>
<td></td>
<td>cT3b</td>
<td>Seminal vesicle invasion</td>
</tr>
<tr>
<td>cT4</td>
<td>Tumor is fixed or invades beyond SV</td>
<td>cT4</td>
<td>Invades bladder neck, muscle, pelvic wall or other</td>
</tr>
</tbody>
</table>
PSA test became widely available in 1988 to measure at ng/mL level

- Demolished false perceptions of treatment efficacy
  - “Is cure possible in those for whom it is necessary — and is cure necessary in those for whom it is possible.” Willet Whitmore, 1990

- Test has only modest sensitivity and specificity
  - Age specific thresholds: 4.0 ng/mL for age 65 – 70
  - PSA velocity in ng/mL/yr
  - PSA density in ng/mL/cm³ of prostate
  - Measure PSA isoforms and precursor molecules
Gleason score is pathological measure of tumor aggressiveness

- Based on glandular architecture of stained tissue viewed at medium microscope power
- Well to poorly differentiated patterns are scored from 1 to 5
  - Two most prevalent patterns are added to create a composite score: e.g. grade 3 + grade 4 = GS 7
  - Distribution of scores by national experts:
    - GS ≤ 4 is rare, less than 1%
    - GS 5 should be about 15% of patients
    - GS 6 – 7 should be about 65%
    - GS 8 – 10 should be about 19%
Gleason grades

Assign a number corresponding to the most predominant glandular differentiation pattern.

Assign a number to secondary foci of disease.

The sum of the patterns is the Gleason score. If there is no secondary pattern, double the primary number.
A commonly used risk group stratification scheme

<table>
<thead>
<tr>
<th>Risk Group</th>
<th>Clinical Stage</th>
<th>PSA</th>
<th>Gleason Score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Low (0)</td>
<td>≤ T2b</td>
<td>≤ 10</td>
<td>≤ 6</td>
</tr>
<tr>
<td>Intermediate (1)</td>
<td>&gt; T2b</td>
<td>or 10</td>
<td>or &gt; 6</td>
</tr>
<tr>
<td>High (≥ 2)</td>
<td>&gt; T2b</td>
<td>and /or 10</td>
<td>and /or &gt; 6</td>
</tr>
</tbody>
</table>
The purpose of risk group stratification

- Indicates likelihood of organ confined disease
  - Low risk: > 2/3
  - Intermediate: 1/3 to 2/3
  - High risk: < 1/3
  - Use Partin tables for accurate values of organ confinement, extracapsular extension, seminal vesicle and lymph node involvement

- Selects patients for the most appropriate therapy
Other selection criteria

- Quality of life factors scored by questionnaires
  - Urinary function: IPSS
  - Erectile function: IIEF
  - Rectal function: RFAS
- Age — older men are at higher risk of failure
- Co-morbidities — patients should have > 5 years life expectancy
- Anatomy — prostates > 100 cm³ are difficult and expensive to implant
How to compare survival across modalities?

- There are no randomized trials comparing surgery, brachytherapy, and external beam
  - SPIRIT closed for lack of accrual despite a $5,000 per patient institutional incentive
- Single institution, multi-modality studies
  - Uniform definition of biochemical survival
  - Uniform risk group classification
    - Other factors such as age differ significantly
  - No report has documented that each therapy modality was delivered to meet a standard of quality
Intermediate risk comparison by treatment modality — Cleveland Clinic
(Ciezki et al. IJROBP 60:1347, 2004)
Single institution comparison by treatment modality
(Sharkey et al. Brachytherapy 4:34-44, 2005)
Inter-institution and inter-modality comparisons

- Averaging data across published reports is subject to selection bias
- Search for the best reported results that have been replicated elsewhere
  - Indicates what is achievable or possible
- Patients stratified by standard risk groups
- Treated in the same era
- At least 100 patients per subgroup analyzed
- Minimum 8 years of follow-up
  - ASTRO and nadir definitions of survival become similar at long follow-up
Low risk, monotherapy survival comparison by treatment modality

- Brachytherapy: 95%
- RP: 88%
- 3DCRT: 80%

Seattle (Blasko)
MSKCC
Fox Chase
Low risk, LDR and HDR brachytherapy survival comparison with XRT boost

Progression Free

Low Risk, Combined Modality

Atlanta (Critz)
Wm Beaumont

Brachytherapy 93%
HDR 92%
Intermediate risk, monotherapy survival comparison by treatment modality

- Brachy 96%
- RP 78%
- 3DCRT 62%

Wheeling
MSKCC
MD Anderson
Intermediate risk, LDR and HDR survival comparison combined with XRT boost

Intermediate Risk, Combined modality

Wm Beaumont Atlanta (Critz)
High risk, monotherapy survival comparison by treatment modality

- **Brachy**: 89%
- **RP**: 59%
- **3DCRT**: 42%

Sites:
- Mt Sinai (NY)
- MSKCC
- Fox Chase
High risk, LDR and HDR survival comparison combined with XRT boost

![Graph showing survival rates for high risk, LDR, and HDR treatments with XRT boost.]

- Brachy 88%
- HDR 70%
- Wheeling, Oakland
Treatment related morbidity

- Every therapy that cures cancer has morbidity
  - A therapy that claims otherwise has not been sufficiently studied, or the proponents are misinformed or quacks

- Morbidity profiles of brachytherapy, surgery, and 3DCRT differ in frequency and intensity for each effect
  - Comparisons between modalities is beyond the scope of this survey
Urinary, rectal and sexual effects

- These side effects appear to follow a critical structure threshold dose response.
  - Below the threshold, the effect is negligible or non-existent

- Structures at risk
  - Prostatic and bulbomembranous urethra
  - Rectal wall
  - Penile bulb
Sagittal schematic of the prostate and nearby structures
Distribution of postimplant day of urinary catheter removal

- Day 0: 92.6%
- Day 1: 3.1%
- Day 2: 1.6%
- Day 3: 0.6%
- Day 4: 0.2%
- > Day 4: 1.9%
Mean IPSS difference from preimplant baseline
(n = 976)
Kaplan-Meier rate of return to preimplant IPSS baseline \((n = 976)\)
Rectal function assessment score over time
(RFAS scale 0 – 36, preimplant mean = 2.6)
Perceived change in bowel function relative to preimplant status

1999 survey
2002 survey

% of patients

Better: 12% 15%
Same: 69% 73%
Worse: 19% 12%

Perceived change in bowel function
Sexual symptoms reported after brachytherapy  (Merrick et al. IJROBP 96:313-319, 2001)
Potency preservation as a function of preimplant IIEF score  (Merrick et al.)
Potency preservation as a function of age at implant (Merrick et al.)
Potency preservation stratified by penile bulb D$_{50}$ dose of 30% of prescribed dose

- D$_{50}$ ≤ 30% Rx 76%
- D$_{50}$ > 30% Rx 32%

p < 0.001